Low Relapse Rate Leads to High Concordance of Sustained Virologic Response (SVR) at 12 Weeks With SVR at 24 Weeks After Treatment With ABT-450/Ritonavir, Ombitasvir, and Dasabuvir Plus Ribavirin in Subjects With Chronic Hepatitis C Virus Genotype 1 Infection in the AVIATOR Study

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In 247 subjects with hepatitis C virus genotype 1 infection treated with the interferon-free regimen of ABT-450/ritonavir, ombitasvir, and dasabuvir plus ribavirin, concordance of a sustained virologic response at 12 and 24 weeks supports the use of the earlier time point as a primary efficacy endpoint for trials of this interferon-free regimen.

Keywords: hepatitis C; direct-acting antivirals; sustained virologic response; concordance.

METHODS

One interferon-free regimen under investigation includes the 3 direct-acting antivirals (DAAs) ABT-450, ombitasvir, and dasabuvir. ABT-450 is an HCV protease inhibitor with nanomolar activity against GT1, identified by AbbVie and Enanta. Co-dosing with ritonavir, a cytochrome P450 3A4 inhibitor, increases peak and trough concentrations and overall drug exposure of ABT-450 and allows once-daily dosing. Ombitasvir (formerly ABT-267) is an HCV NS5A inhibitor with pan-genotypic picomolar activity, and dasabuvir (formerly ABT-333) is a nonnucleoside NS5B RNA polymerase inhibitor active against GT1. AVIATOR (NCT01464827) was a randomized, open-label, multicenter phase 2b trial designed to evaluate the antiviral activity and safety of various combinations of these DAAs, with or without ribavirin, in treatment-naive subjects and prior null responders infected with GT1 HCV [11]. In that study, treatment-naive subjects and peg-IFN/RBV prior null responders with GT1 HCV infection treated for 12 or 24 weeks with the 3 DAAs plus ribavirin achieved SVR24 rates of 95.2% and 92.7%, respectively.

In the present analysis, we evaluated the concordance of SVR24 with viral suppression at weeks 4 and 12 after the end of therapy (SVR4 and SVR12), among the 247 subjects in...
AVIATOR treated with 3 DAAs plus ribavirin for 12 or 24 weeks. We also assessed concordance with viral suppression at week 4 on therapy (rapid virologic response [RVR]), a commonly used predictor of treatment outcome with interferon-based therapy. We performed this analysis on an intention-to-treat population with missing data counted as failure, and on an observed data population, excluding subjects who achieved virologic suppression and were then lost to follow-up prior to posttreatment week 24.

RESULTS

Subjects (N = 247) treated with 3 DAAs plus ribavirin for 12 or 24 weeks were included in the concordance analysis (Supplementary Figure 1). Demographics and baseline characteristics were consistent with those of the full study population, as previously reported [11] (Supplementary Table 1). Of 247 patients, slightly more than half (53.8%) were male, the majority (86.6%) were white, 36.0% were peg-IFN/RBV prior null responders, 19.0% had IL28B genotype CC, and 66.0% were infected with HCV genotype 1a.

The overall rate of SVR24 for the intention-to-treat population of treatment-naive and prior null responders was 93.9%. Rates of RVR, SVR4, and SVR12 were 99.6%, 96.4%, and 95.5%, respectively. A positive response was defined as having HCV RNA less than the lower limit of quantitation (LLOQ) of 25 IU/mL (Roche COBAS TaqMan real-time reverse transcriptase polymerase chain reaction assay version 2.0). Subjects with HCV RNA below the LLOQ 24 weeks posttreatment and at the earlier time point (week 4 of treatment, or 4 or 12 weeks posttreatment) were thus defined as true positives. Subjects who had quantifiable HCV RNA or missing data at 24 weeks posttreatment and at the earlier time point were defined as true negatives. Positive predictive value was defined as the proportion of true-positive subjects among those who achieved RVR, SVR4, or SVR12 (Supplementary Table 2). Negative predictive value was defined as the proportion of true-negative subjects among those who failed to achieve RVR, SVR4, or SVR12 (Supplementary Table 2). Positive predictive values ranged from 94% to 98%; each earlier outcome had a 100% negative predictive value for SVR24 (Table 1). A value of Cohen’s κ >0.8 represents a high degree of reliability between 2 outcomes [12]. In this study, SVR12 and SVR24 were highly correlated, with a Cohen’s κ value of 0.84, indicating that SVR12 defines treatment response as reliably as SVR24. Because almost all subjects achieved on-treatment response, RVR did not predict SVR.

Between week 4 of treatment (RVR assessment) and posttreatment week 4 (SVR4), there were 4 virologic breakthroughs, 2 relapses, and 2 subjects lost to follow-up. There were no relapses after posttreatment week 4. Six additional subjects were lost to follow-up: 2 between posttreatment weeks 4 and 12, and 4 between posttreatment weeks 12 and 24 (Supplementary Figure 2). All subjects achieving SVR4 or SVR12 also achieved SVR24, except for those lost to follow-up. Thus, loss to follow-up accounted for all discordance between SVR rates.

The rate of SVR24 for the observed data population was 97.1%. Rates of RVR, SVR4, and SVR12 were 99.6%, 97.1%, and 97.1%, respectively. As there were no relapses after posttreatment week 4 and up to posttreatment week 24, there is 100% concordance between SVR4 and both SVR4 and SVR12.

DISCUSSION

The concordance analysis presented here was restricted to 1 study with relatively small sample size, which may limit its applicability. Furthermore, this analysis is specific for this investigational DAA regimen, and cannot be extrapolated to other interferon-free regimens. Differences in mechanism of action, number of agents, intrinsic potency, drug exposure, and treatment duration all may impact the concordance of earlier and later time points. Finally, concordance cannot be assumed for subjects infected with HCV genotypes other than GT1, or for subjects with cirrhosis or human immunodeficiency virus coinfection, as these populations were not included in AVIATOR.

The results of this analysis demonstrate high concordance between SVR24 and earlier virologic outcomes assessed among subjects treated with the 3 DAAs plus ribavirin regimen for 12 or 24 weeks in the AVIATOR trial, which is related to the low rate of virologic failure. Achievement of SVR is an important laboratory benchmark, which is associated with a reduced risk of HCV-related cirrhosis, end-stage liver disease, and hepatocellular carcinoma [13].

For interferon-based therapies including a protease inhibitor such as simeprevir, RVR is highly predictive of SVR12 [14–16]. In our analysis, RVR did not predict outcome as virtually all patients achieved this benchmark. Thirty-nine patients with RVR had detectable HCV RNA at week 4, but this finding did not

<p>| Table 1. Concordance With Sustained Virologic Response at 24 Weeks, Intention-to-Treat Population |
|------------------------------------------------|---------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Response</th>
<th>3 DAAs + RBV for 12 or 24 wk (N = 247)</th>
<th>Rate, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Cohen’s κ</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVR</td>
<td></td>
<td>99.6</td>
<td>94.3</td>
<td>100</td>
<td>100</td>
<td>6.7</td>
<td>0.12</td>
</tr>
<tr>
<td>SVR at 4 wk</td>
<td></td>
<td>96.4</td>
<td>97.5</td>
<td>100</td>
<td>100</td>
<td>60.0</td>
<td>0.74</td>
</tr>
<tr>
<td>SVR at 12 wk</td>
<td></td>
<td>95.5</td>
<td>98.3</td>
<td>100</td>
<td>100</td>
<td>73.3</td>
<td>0.84</td>
</tr>
<tr>
<td>SVR at 24 wk</td>
<td></td>
<td>93.6</td>
<td></td>
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</table>

Abbreviations: DAA, direct-acting antiviral; NPV, negative predictive value; PPV, positive predictive value; RBV, ribavirin; RVR, rapid virologic response; SVR, sustained virologic response.
reliably predict treatment outcome; while 4 of these 39 patients failed to achieve SVR12, only 2 were due to treatment failure.

Our results also suggest that HCV RNA monitoring during treatment, which is performed as part of response-guided algorithms to determine treatment duration for some interferon-based regimens [14, 15], may play less of a role in this setting. It is not known whether treatment response at earlier time points (eg, week 1 or week 2) might predict treatment outcome. In addition, long-term follow-up of larger populations of patients would be useful to quantify the risk of very late relapses (after achieving SVR24). Both of these questions are potential areas for future study.

In summary, this analysis supports the use of SVR12 as a primary efficacy endpoint for trials of this interferon-free regimen in subjects with HCV GT1 infection.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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**References**